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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,772	04/10/2000	Tracy D. Wilkins	420522000100	3347

25225 7590 04/24/2006

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/24/2006

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/545,772
Filing Date: April 10, 2000
Appellant(s): WILKINS ET AL.

Tracy D. Wilkins, et al.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 3, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Claims on Appeal

The Appeal involves claims 1,3, 6, 13-15, 19-20, 23-26, 28-31, 36-39 and 62.

(5) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(6) Summary of Invention

The summary of invention contained in the brief is correct.

(7) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

Finality of the last Office Action should be withdrawn.

Claims 1, 3, 6, 13-15, 19-20, 23-24 and 36-39 are unpatentable over Thomas, Jr. et al in view of Schneerson et al under 35 U.S.C. 103(a).

Claims 1, 3, 6, 13-15, 19-20, 25-26 and 36-39 are unpatentable over Thomas, Jr. et al in view of Taylor et al under 35 U.S.C. 103(a).

Claims 1, 3, 6, 13-15, 19-20, 28-29 and 36-39 are unpatentable over Thomas, Jr. et al in view of Devi et al under 35 U.S.C. 103(a).

Claims 1, 3, 6, 13-15, 19, 30-31, 33 and 36-39 are unpatentable over Thomas, Jr. et al in view of Fattom et al under 35 U.S.C. 103(a).

(8) Grouping of Claims

Appellant's brief includes a statement that the claims for each ground of rejection stand or fall together. Appellant also provides reason as set forth in 37 CFR 1.192(c) (7) and (c)(8).

(9) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(10) Prior Art of Record

US 5,919,463, 07/1999. Thomas, Jr. et al.,

Schneerson et al, *Infection and Immunity, Synthesis of Conjugate Vaccine Composed of Pneumococcus Type 14 Capsular Polysaccharide Bound to Pertussis Toxin,* Vol. 60, No. 9, (September 1992) pp. 3528-3532.

Devi et al, Proc. Natl. Acad. Sci. USA, *Antibodies to poly[2→8)-α-N-acetylneuraminic acid and poly[2→9)-α-N-acetylneuraminic acid are Elicited by immunization of mice with Escherichia coli K92 Conjugates: Potential Vaccines for Groups B and C Meningococci and E. Coli K1*, Vol. 88, (August 1991) pp.7175-7179.

Taylor et al, *Infection and Immunity, Synthesis, Characterization, Clinical Evaluation of Conjugate Vaccines Composed of the O-Specific Polysaccharides of Shigella dysenteriae Type 1, Shigella flexneri Type 2a, and Shigella sonnei (Plesiomonas shigelloides) Bound to Bacterial Toxoids*, Vol. 61, No. 9, (September 1993) pp. 3678-3687.

Fattom et al, *Infection and Immunity, Synthesis and Immunologic Properties in Mice of Vaccines Composed of Staphylococcus aureus Type 5 and Type 8 Capsular Polysaccharides Conjugated to Pseudomonas aeruginosa Exotoxin A,* Vol. 58, No.7, (July 1990) pp. 2367-2374).

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. **This issue is not a New Ground of Rejection raised in the Examiner's Answer. This rejection was made in prosecution because the Appellant amended claim 1, which changed the scope of the invention. See Final Office action date May 5, 2004.** This rejection was necessitated by amendment filed **December 11, 2003.** This rejection was set forth because the Appellant amended independent claim 1 (and all claims that depend therefrom) from "... a recombinant protein and a polysaccharide component" to "...a recombinant protein conjugated to a polysaccharide component...". Therefore, the scope of the invention has changed and the amended claims require that the protein and the polysaccharide are conjugated opposed to being mixed together.

In view of the comments made above, this Examiner's Answer does not require the signature of the TC Director.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

II. Claims 1, 3, 6, 13-15, 19-20 and 23-24 and 36-39 are rejected under 35 U.S.C. 103(a) as unpatentable over Thomas, Jr. et al *(U.S. Patent No. 5,919,463, filed October 16, 1995)* in view of Schneerson et al *(Infection and Immunity, September, 1992, p. 3528-3532).*

Claims 1, 3, 6, 13-15, 19-20 and 23-24 and 36-39 are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition is formulated for injection, wherein the pathogenic organism is *Streptococcus pneumoniae*.

Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository) (column 1). Thomas, Jr. et al disclose that the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity (column 1). Thomas, Jr. disclose that the toxins of the invention may be covalently coupled or chemically cross-linked to an antigen by standard methods (column 2). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas, Jr. et al disclose that the compositions of the invention can be administered to a patient using standard methods which include oral, rectal, vaginal, intravenous, subcutaneous, intraperitoneal or intramuscular administration (column 3).

Thomas, Jr. et al do not teach serotype 14 *Streptococcus pneumoniae*.

Schneerson et al teach that the serotype 14 *Streptococcus pneumoniae* capsular polysaccharide is poorly immunogenic among the pneumococcal capsular polysaccharides (page 3528). Schneerson et al teach that the development of polysaccharide protein conjugates for prevention of systemic infection caused by *Haemophilus influenzae* type b serves as a precedent for making conjugates of polysaccharides of other capsulated pathogens (page 3528). Schneerson teach that conjugation of antigen to improve the immunological properties of other polysaccharides

such as *Streptococcus pneumoniae* have been used (page 3528). Schneerson et al teach a conjugate vaccine composed of serotype 14 *Streptococcus pneumoniae* capsular polysaccharide (PN14) bound to Pertussis Toxin. Schneerson et al teach that Pertussis toxin is both a virulence factor and protective antigen of *Bordetella pertussis*. Schneerson et al devised a synthetic scheme to prepare a conjugate of serotype 14 *Streptococcus pneumoniae* and Pertussis toxin. Schneerson et al further teach that the serotype 14 *Streptococcus pneumoniae*-Pertussis toxin conjugate elicited antibodies in mice to serotype 14 *Streptococcus pneumoniae* at levels estimated to be protective in humans and elicited neutralizing antibodies to Pertussis toxin (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the serotype 14 *Streptococcus pneumoniae* capsular polysaccharides of Schneerson et al to the immunogenic composition as taught by Thomas, Jr. et al because Schneerson et al demonstrates that serotype 14 *Streptococcus pneumoniae* capsular polysaccharides are poorly immunogenic, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (3528). It would be expected, barring evidence to the contrary, that an immunogenic composition comprising the serotype 14 *Streptococcus pneumoniae* capsular polysaccharides of Schneerson et al and the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity of Thomas, Jr. et al would be effective in protecting against a pathogenic microorganism because Schneerson et al teach that covalent attachment of PN14 to protein conferred enhanced immunogencity and T cell dependence (page 3530). Additionally, Thomas,

Jr. et al teach that ARU when added to antigen leads to effective mucosal immune responses (column 1).

III. Claims 1, 3, 6, 13-15, 19-20, 25-26 and 36-39 as unpatentable over Thomas, Jr. et al *(U.S. Patent No. 5,919,463, filed October 16, 1995)* in view of Taylor et al *(Infection and Immunity, September 1993, p. 3678-3687).*

Claims 1, 3, 6, 13-15, 19-20, 25-26 and 36-39 are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition is formulated for injection, wherein the pathogenic organism is *Shigella flexneri.*

Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridium difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository) (column 1). Thomas, Jr. et al disclose that the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity (column 1). Thomas, Jr. disclose that the toxins of the invention may be covalently coupled or chemically cross-linked to an antigen by standard methods (column 2). Thomas, Jr. et al disclose that intranasal

administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas, Jr. et al disclose that the compositions of the invention can be administered to a patient using standard methods which include oral, rectal, vaginal, intravenous, subcutaneous, intraperitoneal or intramuscular administration (column 3).

Thomas, Jr. et al do not teach *Shigella flexneri* Type 2a.

Taylor et al teach a conjugate vaccine comprising *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* bound to bacterial toxoids (carrier proteins). Taylor et al teach that *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* administered to mice alone are not immunogenic. Taylor et al further teach that *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* conjugated to a carrier protein injected into mice subcutaneously in saline solutions elicited serum IgG and IgM antibodies with booster responses. When the *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* conjugate were adsorbed with alum further enhancement of their immunogenicity was observed (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the *Shigella flexneri* 2a capsular polysaccharides of Taylor et al to the immunogenic composition as taught by Thomas, Jr. et al because Taylor et al teach that *Shigella flexneri* 2a capsular polysaccharides are poor immunogens when administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (the entire article). It would be expected, barring

evidence to the contrary, that an immunogenic composition comprising the *Shigella flexneri* 2a capsular polysaccharides of Taylor et al and the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity of Thomas, Jr. et al would be effective in protecting against a pathogenic microorganism because Taylor et has demonstrated that capsular polysaccharides conjugated to carrier proteins injected into mice elicited serum IgG and IgM antibodies with booster responses and adsorption onto alum enhanced immunogenicity (see the Abstract). Taylor et al teach that *Shigella flexneri* 2 a conjugates conferred protective levels of IgG antibodies (page 3684). Additionally, Thomas, Jr. et al teach that ARU when added to antigen leads to effective mucosal immune responses (column 1).

IV. Claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 62 are rejected under 35 U.S.C. 103(a) as unpatentable over Thomas, Jr. et al *(U.S. Patent No. 5,919,463, filed October 16, 1995)* in view of Devi et al *(Proc. National Academy of Science, Volume 88, August 1991, p. 7175-7179).*

Claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 62 are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition is formulated for injection, wherein the pathogenic organisms are *Escherichia coli* and *Neisseria meningitidis.*

Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridium difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository) (column 1). Thomas, Jr. et al disclose that the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity (column 1). Thomas, Jr. disclose that the toxins of the invention may be covalently coupled or chemically cross-linked to an antigen by standard methods (column 2). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas, Jr. et al disclose that the compositions of the invention can be administered to a patient using standard methods which include oral, rectal, vaginal, intravenous, subcutaneous, intraperitoneal or intramuscular administration (column 3).

Thomas, Jr. et al do not teach *Escherichia coli* K1 or *Neisseria meningitidis* serogroup B.

Devi et al teach that the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are identical (poly{(2→8)-α-N-acetylneuaminic acid)} or poly(α2-8NeuNAc) and serve as essential virulence factors and protective antigens for both pathogens. Devi et al teach that capsular polysaccharides are poor immunogens when administered alone, but conjugating these capsular polysaccharides to tetanus toxin (carrier proteins) enhances their immunogenicity (the Abstract).

Devi et al teach that attempts have been made to induce protective immunity to *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B have been thwarted because poly(α2-8NeuNAc), alone or complexed to outer membrane proteins induced low transient levels of IgM antibodies (page 7175). Devi et al teach that when the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are conjugated to tetanus toxin (a carrier protein) and injected into mice in a saline solution the capsular polysaccharides elicit both poly(α2-8NeuNAc) IgM and IgG antibodies. Devi et al further teach that re-injection elicited booster responses of both isotypes (T-dependent properties) at dosages applicable for clinical use (page 7178).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B as taught by Devi et al to the immunogenic composition as taught by Thomas, Jr. et al because Devi et al teach that capsular polysaccharides are poor immunogens when administered alone, but conjugating these capsular polysaccharides to tetanus toxin (carrier proteins) enhances their immunogenicity (the entire article). It would be expected, barring evidence to the contrary, that an immunogenic composition comprising the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B as taught by Devi et al and the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity of Thomas, Jr. et al would be effective in protecting against a pathogenic microorganism because Devi et al demonstrated that *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B antigens when conjugated

to tetanus toxoid elicited 90.% and 100% IgG antibodies, respectively (see Table 4, page 7178). Additionally, Thomas, Jr. et al teach that ARU when added to antigen leads to effective mucosal immune responses (column 1).

V. Claims 1, 3, 6, 13-15, 19, 30-31, 33 and 36-39 are rejected under 35 U.S.C. 103(a) as unpatentable over Thomas, Jr. et al *(U.S. Patent No. 5,919,463, filed October 16, 1995)* in view of Fattom et al *(Infection and Immunity, July 1990, 2367-2374).*

Claims 1, 3, 6, 13-15, 19, 30-31, 33 and 36-39 are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition is formulated for injection, wherein the pathogenic organism is *Staphylococcus aureus.*

Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository) (column 1). Thomas, Jr. et al disclose that the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity (column 1). Thomas, Jr. disclose that the toxins of the invention may be covalently coupled or chemically cross-linked to an antigen by standard methods (column 2). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper

respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas, Jr. et al disclose that the compositions of the invention can be administered to a patient using standard methods which include oral, rectal, vaginal, intravenous, subcutaneous, intraperitoneal or intramuscular administration (column 3).

Thomas, Jr. et al do not teach *Staphylococcus aureus* Type 5 or Type 8 capsular polysaccharides.

Fattom et al teach vaccines composed of *Staphylococcus aureus* type 5 and Type 8 capsular polysaccharides conjugated to *Pseudomonas aeruginosa* Exotoxin A. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are virulence factors and protective antigens for bacteremia caused by *Staphylococcus aureus* (page 2368). Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are poor immunogens in humans when administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity both for active immunization and for preparing high-titered antisera in volunteers for passive immunization (page 2368). Fattom et al teach that when *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are bound to a protein (i.e. *Pseudomonas aeruginosa* exotoxin A) to form a conjugate both *Staphylococcus aureus* type 5 and type 8 elicit antibody responses. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides acquire T-cell dependent properties as shown by their ability to respond to carrier priming and thus stimulate booster responses (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides of Fattom et al to the immunogenic composition as taught by Thomas, Jr. et al because Fattom et al teach that the *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are poor immunogens in humans when administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity both for active immunization and for preparing high-titered antisera in volunteers for passive immunization (page 2368). It would be expected, barring evidence to the contrary, that an immunogenic composition comprising the *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides and the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity of Thomas, Jr. et al would be effective in protecting against a pathogenic microorganism because Fattom et al teach that the *Staphylococcus aureus* type 5 and type 8 capsular polysaccharide conjugated elicited as rise in CP antibodies and both S. aureus CPs acquired T cell dependent properties as shown by their ability to respond to carrier priming and to stimulate booster responses (see the Abstract). Fattom et al teach that clinical studies the two conjugates were effective in both active and passive immunization (see the Abstract). Additionally, Thomas, Jr. et al teach that ARU when added to antigen leads to effective mucosal immune responses (column 1).

(11) Response to Arguments

Response to Arguments Traversing to Appellant's assertion that the Finality of the Final Office Action should be withdrawn.

Appellant urges that the finality of the Final Office action (mailed May 2, 2004) action be withdrawn. Appellant urges that the claims were amended from "... a recombinant protein and a polysaccharide component" to "...a recombinant protein conjugated to a polysaccharide component..." and rejections under 35 U.S.C. 103(a) set forth by this amendment were nearly identical to the rejections under U.S.C. 103(a) presented in the Office action dated November 26, 2002. Appellant urges that it is clear that the new rejections were not necessitated by the amendment. Appellant urges that with regard to the amendment to include "an antigen", Appellants submit that "an antigen" does not add subject matter but rather clarifies the phrase "polysaccharide component is characteristic of a pathogenic microorganism".

Before Applicant's amendment filed December 11, 2003, the claims were drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is characteristic of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition is formulated for injection. The Examiner interprets this invention as an immunogenic composition that comprised two components: a) a recombinant protein

(comprising toxin A repeating units) and b) a polysaccharide. There is no limitation in this claim that requires that the recombinant protein and the polysaccharide components are conjugated. In Appellant's amendment submitted to the Office on December 11, 2003, the claims were amended to recite an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition is formulated for injection. With the submission of this amendment Applicant has changed the scope of the claims and now the claims require that the recombinant protein and the polysaccharide components are conjugated to one another which involves different steps than just mixing the two components together. It is well known in the art that conjugation involves covalently coupling a polysaccharide component to a protein carrier using methods such as carbodiimide-mediated condensation or other coupling methods known in the art. The steps of chemically binding the polysaccharide component to the carrier protein involves mixing the polysaccharide and protein carrier with 1-ethyl-3-dimethylaminopropyl, allowing the mixture to dialyze, centrifuging the mixture, equilibrating the mixture in a Sepharose column and filtering the conjugates through a sterile filter.

It should be noted that a telephonic interview was held between Appellant and the Office on June 24, 2003 (before submission of the amendment filed December 11,

2003) and the Appellant stated in the telephonic interview that " the essence of the claimed invention was an immunogenic composition that comprises a protein and a polysaccharide component wherein the protein comprises rARU and the polysaccharide is not conjugated to the protein or a carrier protein". Therefore, it is the position of the Examiner that the new grounds of rejection that were set forth in the Final Office action mailed May 5, 2004 were necessitated by Appellant's amendment and the finality of the Final Office action should be maintained.

Response to Arguments Traversing the Rejection of Claims 1, 3, 6, 13-15, 19-20 and 23-24 and 36-39 under 35 U.S.C. 103(a) as unpatentable Thomas, Jr. et al in view of Schneerson et al.

Appellant urges that in the four obviousness rejections the Examiner combined Thomas, Jr. et al with each of the four secondary references that independently discloses the use of a particular polysaccharides in a formulation for injection. Appellant urges that there is no motivation to modify or combine the references. Appellant urges that Thomas, Jr. et al does not direct a skilled artisan to select the species of rARU to be used as a antigen nor does Thomas, Jr. et al direct a skilled artisan to select the species of rARU to be used as a carrier with polysaccharide antigen. Appellant urges that only by the benefit of the Appellant's disclosure that one could select rARU derived from the repeat units of C. difficile from the genus toxins disclosed by Thomas, Jr. et al. Appellant urges that the use of rARU as an adjuvant is not sufficiently limited or well-delineated to encompass the specific combination of a polysaccharide and rARU.

Appellant urges that Thomas, Jr. et al do not teach the claimed polysaccharides or any other antigens that are not different for *C. difficile* antigens. Applicant urges that Thomas, Jr. et al do not direct a skilled artisan to select a composition formulated for injection comprising a polysaccharide and rARU. Appellant urges that only by the benefit of Appellant's disclosure leads one to select compositions related to Toxin A of C. difficile formulated for injection. Appellant urges that Thomas, Jr. et al only teach in the Examples of the disclosure C. difficile adjuvants in the context of vaccines designed for mucosal administration. Appellant urges that Examples I, I, IVA , IVB and V all disclose compositions formulated for mucosal administration. Appellant urges that the secondary references do not overcome these deficiencies. Appellant urges that the Examiner appears to improperly generalize some disclosure in each of the secondary reference, perhaps in an attempt to establish an expectation of success. Appellant urges that Schneerson et al demonstrates that "conjugating these capsular polysaccharides to proteins enhances their immunogenicity. Applicant urges that there is no such disclosure in the reference.

The claims are directed to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile* wherein said composition if formulated for injection. It is the Examiner's position that Appellant argues the references individually without clearly addressing the

combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Thomas, Jr. et al teach *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity (column 1). Thomas Jr., et al define an adjuvant as a material that when administered with an antigen increases an immune response to the antigen (column 1)(enhances immunogenicity). Thomas, Jr. disclose that the toxins of the invention may be covalently coupled or chemically cross-linked to an antigen by standard methods (column 2). Thomas, Jr. et al teach that the ARU of the invention can be made recombinantly, synthetically or by proteolytic methods (column 2). The Examiner agrees with Appellant that Thomas, Jr. et al do not specially teach the serotype 14 *Streptococcus pneumoniae* capsular polysaccharide. However, Schneerson et al teach a serotype 14 *Streptococcus pneumoniae* capsular polysaccharide and further teach that the serotype 14 *Streptococcus pneumoniae* capsular polysaccharide is poorly immunogenic. One of ordinary skill in the art would have been motivated to select and combine the serotype 14 *Streptococcus pneumoniae*

capsular polysaccharide as taught by Schneerson et al with the ARU of Thomas, Jr. et al because Schneerson et al demonstrates that 14 *Streptococcus pneumoniae* capsular polysaccharides are poorly immunogenic, but conjugating these capsular polysaccharides to carrier proteins enhances their immunogenicity (page 3528) and Thomas, Jr. et al teach *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity. The Examiner disagrees with Appellant's assertion that "Thomas, Jr. et al do not teach that compositions can be formulated for injection". Although, Examples I, II, IVA, IVB and V teach compositions formulated for mucosal administration, Thomas, Jr. et al teach intramuscular administration as well as a number of other modes of administration (column 3). Therefore, compositions formulated for injection are contemplated by the invention. To address Appellant's argument regarding expectation of success, Thomas, Jr. et al teach that any antigen can be administered with the adjuvant (ARU) of the invention (columns 2-3) and Schneerson et al has demonstrated success in conjugating polysaccharides to carrier proteins.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Response to Arguments Traversing the Rejection of Claims 1, 3, 6, 13-15, 19-20 and 25-26 and 36-39 under 35 U.S.C. 103(a) as unpatentable Thomas, Jr. et al in view of Taylor et al.

Appellant argues in regards to Thomas, Jr. et al the same as in the arguments set forth above and the Examiner has addressed these arguments above. Additionally, Appellant urges that Taylor et al describes polysaccharide conjugates of *Shigella* polysaccharides with bacterial toxoids. Appellant urges that the Examiner alleges that Taylor et al teach that "conjugating in these capsular polysaccharides to protein enhances their immunognicity". Appellant urges that Taylor et al describes two protein conjugates, *Pseudomoans aeruginosa* exoprotein A (rEPA) and tetanus toxoid (TT) and although the Abstract refers to the polysaccharides as covalently bound to carrier proteins, it appears that the article describes rEPA and TT rather than carrier proteins in general. Appellant urges that even if the authors intended to suggest that any carrier protein would be effective such suggestion would be obvious to try in a conjugate.

The Examiner has addressed Appellant's arguments in regards to Thomas, Jr. et al above. To address Appellant's comments in regards to Taylor et al, it is the Examiner's position that Taylor et al teach that rEPA and TT are carrier proteins and the polysaccharides of *Shigella dysenteriae* Type 1, *Shigella flexneri* Type 2a and *Shigella sonnei* must be bound to a carrier protein to elicited serum IgG and IgM antibody responses. Taylor et al further teach that the conjugates, which are polysaccharides

covalently bound to carrier proteins (specifically rEPA or TT) adsorption onto alum has enhanced immunogenicity. The teachings of Thomas, Jr. et al have been described above. Thomas, Jr. et al do not specifically teach polysaccharides of *Shigella dysenteriae* Type 1, *Shigella flexneri* Type 2a and *Shigella sonnei.* One of ordinary skill in the art would be motivated to select and conjugate the *Shigella dysenteriae* Type 1, *Shigella flexneri* Type 2a and *Shigella sonnei* polysaccharides as taught by Taylor et al to the ARU of Thomas, Jr. et al because Taylor et al have demonstrated that polysaccharides poorly immunogenic when administered alone and immunogenicity is enhanced when coupled to a carrier protein (page 3678) and Thomas, Jr. et al has taught that the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity. To address Appellant's comments regarding "obvious to try", Taylor et al has demonstrated that carrier proteins work effectively with polysaccharides to elicit serum antibody responses.

Response to Arguments Traversing the Rejection of Claims 1, 3, 6, 13-15, 19-20 and 28-29, 36-39 and 62 are rejected under 35 U.S.C. 103(a) as unpatentable Thomas, Jr. et al in view of Devi et al.

Appellant argues in regards to Thomas, Jr. et al the same as in the arguments set forth above and the Examiner has addressed these arguments above. Additionally, Appellant urges that Devi et al describes polysaccharide conjugates of capsular polysaccharides from *N. meningitidis* and *E. coli* with tetanus toxoid. Appellant urges that the Examiner alleges that Devi et al teach that "conjugating in these capsular polysaccharides to protein enhances their immunognicity". Appellant urges that the

Devi et al Abstract does not extrapolate its tetanus toxin/polysaccharide conjugate results to conjugates comprising carrier proteins in general. Appellant urges that even if the authors intended to suggest that any carrier protein would be effective such suggestion would be obvious to try in a conjugate.

The Examiner has addressed Appellant's arguments in regards to Thomas, Jr. et al above. To address Appellant's comments in regards to Devi et al, it is the Examiner's position that Devi et al teach conjugates of capsular polysaccharides from *N. meningitidis* and *E. coli* with tetanus toxoid. Devi et al teach that capsular polysaccharide complex alone is poorly immunogenic (see the Abstract) and the polysaccharides were conjugated to a protein carrier (specifically tetanus toxoid) immunogencity is enhanced. The teachings of Thomas, Jr. et al have been described above. Thomas, Jr. et al do not specifically teach polysaccharides of *E. coli* K92 and *N. meningitidis* serogroup B. One of ordinary skill in the art would be motivated to select and conjugate the polysaccharides as taught by Devi et al to the ARU of Thomas, Jr. et al because Devi et al has demonstrated that polysaccharides poorly immunogenic when administered alone and immunogenicity is enhanced when coupled to a carrier protein (page 7175) and Thomas, Jr. et al has taught that the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity. To address Appellant's comments regarding "obvious to try", Devi et al has demonstrated that carrier proteins work effectively with polysaccharides to elicit serum antibody responses.

Response to Arguments Traversing the Rejection of Claims 1, 3, 6, 13-15, 19, 30-31, 33, 36-39 and 62 are rejected under 35 U.S.C. 103(a) as unpatentable Thomas, Jr. et al in view of Fattom et al.

Appellant argues in regards to Thomas, Jr. et al the same as in the arguments set forth above and the Examiner has addressed these arguments above. Additionally, Appellant urges that Fattom et al describes a conjugate of capsular polysaccharides from *S. aureus* and a *P. aeruginosa* exotoxin A. Appellant urges that the Examiner alleges that Fattom et al teach "conjugating in these capsular polysaccharides to protein enhances their immunognicity". Appellant urges that there is no generalization that the conjugating polysaccharides to proteins would other than exotoxin A would have an effect. Appellant urges that even if the authors intended to suggest that any carrier protein would be effective such suggestion would be obvious to try in a conjugate.

The Examiner has addressed Appellant's arguments in regards to Thomas, Jr. et al have been discussed above. To address Appellant's comments in regards to Fatton et al, it is the Examiner's position that Fattom et al teach conjugates of capsular polysaccharides composed of *Staphyloccoccus aureus* Type 5 and Type 8 and exotoxin. Fattom et al teach that capsular polysaccharides alone are poorly immunogenic (page 2367-2368) and the polysaccharides were conjugated to a protein carrier (specifically exotoxin A) immunogencity is enhanced. The teachings of Thomas, Jr. et al have been described above. Thomas, Jr. et al do not specifically teach polysaccharides of *Staphylococcus aureus* Type 5 and Type 8. One of ordinary skill in the art would be motivated to select and conjugate the polysaccharides as taught by

Fattom et al to the ARU of Thomas, Jr. et al because Fattom et al has demonstrated that polysaccharides poorly immunogenic when administered alone and immunogenicity is enhanced when coupled to a carrier protein (pages 2367-2368) and Thomas, Jr. et al has taught that the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity. To address Appellant's comments regarding "obvious to try", Fattom et al has demonstrated that carrier proteins that work effectively with polysaccharides to elicit serum antibody responses.

Examiner's Answer Conclusion

For the above reasons, it is believed Examiner should be affirmed.

Respectfully submitted,

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April 6, 2006

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